PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Lippman, et al
Serial Number 08/096,277
Filed: July 26 1993

Group Art Unit: 1813
Examiner: Kim
Atty. Docket: 2899.43360

For: LIGAND GROWTH FACTORS THAT BIND TO THE ERBB-2 RECEPTOR PROTEIN AND INDUCE CELLULAR RESPONSES

AMENDMENT A

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

The following amendments are submitted in response to the Office Action mailed on September 19, 1994. A Petition for Extension of Time is enclosed to extend the time for response to March 19, 1995. Our check in the amount of four hundred thirty-five dollars ($435.00) is enclosed to cover the extension fee. It is believed that no other fees are required to make this response complete and timely; however, should it be determined that any additional fees are required, the Commissioner is authorized to charge such fees to our Deposit Account No. 19-0733.

Please make the following amendments in the subject application.

IN THE SPECIFICATION

Please insert the following material representing pages 68 and 69 of the application between pages 67 and 70 of the specification.

TGFα-like polypeptide on these cells were similar to those observed with EGF and TGFα.

EXAMPLE 9.

The biological activity of the purified 30 kDa TGFα-like factor was further assessed by examining its ability to induce autophosphorylation of the EGF receptor. A431 cells, which overexpress the EGF receptor, were incubated with various concentrations of EGF, TGFα or TGFα-like growth factors. Each of the three peptides similarly stimulated phosphorylation of the EGF receptor.

Phosphorylation of the EGF Receptor

Subconfluent A431 cells were cultured in IMEM for 10-12 hours. The cells were treated with 10-30 nM TGFα, EGF or TGFα-like growth factor for 30 minutes at 37°C. Cells were lysed in 20 mM Tris-HCl (pH 7.4), 150 mM NaCl, 1% NP40, 1 mM EDTA, 2 mM PMSF, 42 mM leupeptin and immunoprecipitated as described above using monoclonal antibody 225 directed against the EGF receptor (Oncogene Science, Manhasset, NY). The immunoprecipitates were washed three times with RIPA buffer and resuspended in 40 1 TNE (0.01M Tris-HCl, pH 7.5, 0.15 M NaCl, 1 mM EDTA). Five Ci of [γ-^{32}P] ATP was added to the immuno-precipitates and the total ATP concentration was adjusted to 15 mM (final) in a volume of 60 1. The reaction mixture was incubated for 5 minutes on ice before addition of 20 1 of 3x sample buffer. The samples were boiled for 5 minutes and analyzed by denaturing 7.5% SDS-PAGE.

105

EXAMPLE 10.

In order to characterize the cellular effects of the present 30 kDa glycoprotein ligand, its induction of tyrosine phosphorylation was assessed in the human breast cancer lines MDA-MB-468 and SK-Br-3. Notably, MDA-MB-468 cells have amplification and over expression of the EGFR gene and do not express erbB-2 receptor-like protein. SK-Br-3 cells have amplification and over expression of the erbB-2 gene as well as relatively elevated levels of EGFR.

- 69 -

Detection of Phosphorylated Proteins in SK-Br-3 Cells

SK-Br-3 cells were grown in 90% confluence in 24-well plates (Costar). Cells were treated at 30°C with IMEM (Figure 2, lanes 1 and 2), IMEM containing 25 nb/ml recombinant TGFα (Genentech, CA) (Figure 2, lanes 3 and 4), and IMEM containing 5 ng/ml of gp30 (Figure 2, lanes 5 and 6), all of these in the presence (Figure 2, lanes 1, 4, 5) and the absence (Figure 2, lanes 2, 3, 6) of an anti-EGF receptor blocking antibody (Genetech, CA). After 20 minutes the media was removed and cells were lysed in 100 μl of sample buffer containing 1% SDS, 0.1% β-mercaptoethanol, 0.15 M Tris-HCl (pH 6.8), 10% glycerol, 0.02% bromophenol-blue, 1mM EDTA, 2 mM PMSF and 42 mM leupeptin. After 5 minutes at 95°C, 50 μg of protein were loaded in a 7.5% SDS-PAGE. Proteins were then transferred to nitrocellulose membrane for immunoblotting (Hoefer Scientific Instruments, California) by electrophoresis in a modified method of Towbin, et al., using an electrophoretic transfer unit (Hoefer, TE 22). Electrophoretic transfer was carried out at room temperature for one hour at 125 mA in a buffer containing 25 Mm glycine, 129 Mm Tris (Ph 8.3) and 20% methanol. Following transfer, the filter was blocked with 5% BSA in Tris-Buffered Saline containing 0.5%

106

Tween 20. An antiphosphotryosine antibody (Amersham) was reacted with the immobilized proteins in 5% BSA (Sigma RIA Grade). Immunocomplexes were detected by a goat anti-mouse antibody conjugated to alkaline phosphatase. Blots were then incubated with a color development substrate solution containing NBT and BCIP (Promega).

B1

Alternatively, cells were grown to 80% confluence in a 35 mm dish (Costar). FCS was removed 16 hours prior to the labelling. Cells were rinsed with [PO_4] free DMEM (GIBCO) and then incubated for 3 hrs at 37°C with 1.0 mCi/ml of [^{32}Pi]/dish (32-orthophosphate Amersham). After 3 hrs, cells were treated for 20 minutes at 37°C with different samples (which includes gp30). Following the incubation the culture dishes were placed over an ice-bath and the cells were washed twice with PBS. Lysates were prepared with a modified Ripa buffer, containing 1% Triton X100, kinase, protease and phosphatase inhibitors, at 4°C.

IN THE CLAIMS

Please cancel claims 6-8, 11-12, 17-18, 22, 28-32, 35, 38-39, and 43. Please amend claims 1-5, 9, 13, 15-16, 19-21, 23-24, 26, 33, 36-27, 40-41, and 44-45 as follows.

B2

1. (Amended) A substantially pure protein [erbB-2 ligand], wherein said [ligand is capable of binding to erbB-2 receptor protein (p185^{erbB-2})] protein:

binds to heparin-Sepharose;

has apparent molecular weight as measured by SDS PAGE of about 30 kDa ;

has apparent molecular weight as measured by SDS PAGE of about 22 kDa after N-glycanase digestion;

107

has an amino acid sequence which corresponds to the sequence of a peptide of approximately 22 kDa molecular weight as measured by SDS PAGE produced by *in vitro* translation of poly A RNA from MDA-MB-231 cells;

B2 upon hydrolysis with *S. aureus* V8 protease or elastase produces a peptide pattern substantially the same as that produced by the same protease from a peptide of approximately 22 kDa molecular weight as measured by SDS PAGE produced by *in vitro* translation of poly A RNA from MDA-MB-231 cells; and

is immunoprecipitated by anti-TGF-α antisera.

2. (Amended) The substantially pure [erbB-2 ligand of] protein according to claim 1, wherein said [ligand has a molecular weight of about 30 kDa, is capable of inducing phosphorylation of $p185^{erbB-2}$ and is capable of inhibiting proliferation of adenocarcinomal cells] protein:

induces phosphorylation of $p185^{erbB-2}$ in cells that overexpress erbB-2;

induces internalization of the erbB-2 receptor;

stimulates growth of cells which overexpress erbB-2;

inhibits growth of cells that overexpress erbB-2;

reverses Mab 4D5-dependent inhibition of erbB-2 overexpressing cells;

induces differentiation of erbB-2 overexpressing cells; and

stimulates phosphorylation of epidermal growth factor receptor (EGFR) in EGFR expressing cells.

3. (Amended) The substantially pure [erbB-2 ligand of] protein according to claim 1, [wherein said ligand corresponds to the $p185^{erbB-2}$-binding protein of MDA-MB-231 cells] said

protein having an amino acid sequence which corresponds to an amino acid sequence encoded by the DNA sequence of Figure 18A, Figure 18B, Figure 23B, or a fragment thereof.

4. (Amended) The substantially pure [erbB-2 ligand of] protein according to claim 1, [wherein said ligand is not capable of binding to epidermal growth factor receptor (EGFR)] said protein having the same sequence as a peptide of approximately 22 kDa molecular weight as measured by SDS PAGE produced by *in vitro* translation of poly A RNA from MDA-MB-231 cells.

5. (Amended) A substantially pure protein [The substantially pure erbB-2 ligand of claim 1], wherein said [ligand] protein:

~~reverses Mab 4D5 dependent inhibition of erbB-2 overexpressing cells;~~

reverses antiproliferative effect of soluble erbB-2 extracellular domain (ECD);

inhibits cell proliferation and colony formation of cells which overexpress erbB-2;

has [a] apparent molecular weight as measured by SDS PAGE of about 75 kDa;

is capable of inducing phosphorylation of $p185^{erbB-2}$; and

[is capable of inhibiting proliferation of adenocarcinoma cells]

does not bind EGFR.

9. (Amended) A method of inhibiting the growth of cells which overexpress the oncogene erbB-2 or EGFR comprising treating said cells with an amount of [erbB-2 ligand] the substantially pure protein according to claim 1 which is effective to inhibit the growth of said cells.

10. The method of claim 9, wherein said cells are adenocarcinoma cells.

13. (Amended) A method of inhibiting the growth of cells ~~which overexpress~~ in vitro the oncogene ~~erbB-2 or EGFR~~ comprising treating said cells in vitro with an amount of [erbB-2 ligand] the substantially pure protein according to claim 5 which is effective to inhibit the growth of said cells.

14. The method of claim 13, wherein said cells are adenocarcinoma cells.

15. (Amended) A method of stimulating the growth of normal or malignant erbB-2 over-expressing adenocarcinoma cells comprising treating said cells with an amount of [erbB-2 ligand] the substantially pure protein according to claim 1 which is sufficient to stimulate the growth of said cells.

16. (Amended) The method of claim 15, wherein said cells are adenocarcinoma cells or other [malignancies shown to be overexpressing] malignant cells which overexpress erbB-2.

19. (Amended) A method of stimulating the growth of normal or malignant erbB-2 over-expressing ~~adenocarcinoma~~ cells in vitro comprising treating said cells in vitro with an amount of [erbB-2 ligand] the substantially pure protein according to claim 5 which is sufficient to stimulate the growth of said cells.

20. (Amended) The method of claim 19, wherein said cells are adenocarcinoma cells ~~or other [malignancies shown to be overexpressing] malignant cells which overexpress erbB-2.~~

21. (Amended) An antibody which specifically binds the protein [erbB-2 ligand] of claim 1.

23. (Amended) An antibody which specifically binds the protein [erbB-2 ligand] of claim 5.

109

24. (Amended) A method of inhibiting the growth of cells which overexpress the oncogene erbB-2 or EGFR comprising treating said cells with an amount of antibody according to claim 21 or claim 23 which is effective to inhibit the growth of said cells.

25. The method of claim 24 wherein said antibody is conjugated to a therapeutic agent.

26. (Amended) A method of stimulating the growth of normal or malignant erbB-2 over-expressing adenocarcinoma cells comprising treating said cells with an amount of antibody according to claim 21 or claim 23 which is sufficient to stimulate the growth of said cells.

27. The method of claim 26 wherein said antibody is conjugated to a therapeutic agent.

33. (Amended) A method of detecting the presence of [erbB-2 ligand expressing] cells expressing the protein according to claim 1 in a patient comprising:

a. contacting a sample obtained from said patient with a detectably labeled antibody [according to claim 21] which specifically binds said protein for a time sufficient for binding between said antibody and [erbB-2 ligand] said protein; and

b. detecting the presence of [erbB-2 ligand] said protein bound to said antibody in said sample.

34. The method of claim 33, wherein said sample is selected from the group consisting of body tissue, blood, urine, saliva, tear drops, serum, cerebrospinal fluid and feces.

36. (Amended) A method of detecting the presence of [erbB-2 ligand expressing] cells expressing the protein according to claim 5 in a patient comprising:

a. contacting a sample obtained from said patient with a detectably labeled antibody [according to claim 21] which specifically binds said protein for a time sufficient for binding between said antibody and [erbB-2 ligand] said protein; and

b. detecting the presence of [erbB-2 ligand] said protein bound to said antibody in said sample.

B8

37. (Amended) A method for purifying [an erbB-2 ligand] the protein of claim 1 from a contaminate solution thereof, comprising binding said protein to immobilized heparin and subsequently eluting said protein from said heparin.

40. (Amended) A method of preparing a substantially pure [erbB-2 ligand] protein according to claim 1 or claim 5, comprising:

B9

a) producing a cDNA library corresponding to mRNA from a cell line that expresses [erbB-2 ligand] said protein and selecting clones from the library based on ability to hybridize with probes encoding a portion of the sequence of [the erbB-2 ligand of claim 1] said protein;

b) transforming a host cell with DNA from the selected clones;

c) growing the transformed host cell in culture; and

d) recovering [erbB-2 ligand] said protein from the culture.

41. (Amended) A method for obtaining an isolated DNA molecule encoding [an erbB-2 ligand] the protein of claim 1, comprising:

a) constructing DNA probes which encode a portion of the sequence of [an erbB-2 ligand according to claim 2] said protein;

b) constructing a cDNA library from mRNA extracted from a cell line that expresses [an erbB-2 ligand] said protein;

B9

c) selecting from said cDNA clones containing DNA which hybridizes to said DNA probes; and

d) isolating the DNA from the selected clones.

42. An isolated DNA molecule obtained by the method of claim 41.

44. (Amended) An isolated DNA molecule [obtained by the method of claim 43] having a sequence found in Figure 18A, Figure 18B, or Figure 23B, or a variant or fragment thereof.

B10

45. (Amended) A method for obtaining an isolated DNA molecule encoding [an erbB-2 ligand] the protein of claim 5, comprising:

a) constructing DNA probes which encode a portion of the sequence of [an erbB-2 ligand according to claim 5] said protein;

b) constructing a cDNA library from mRNA extracted from a cell line that expresses [an erbB-2 ligand] said protein;

c) selecting from said cDNA clones containing DNA which hybridizes to said DNA probes; and

d) isolating the DNA from the selected clones.

46. An isolated DNA molecule obtained by the method of claim 45.

REMARKS

Restriction under 35 U.S.C. 121

In response to the Restriction Requirement imposed in the above-named application, Applicants traverse the Requirement, but affirm their provisional election of claims 1-20 as required in the Office Action. Applicants point out that Group V represents a method for producing the protein of Group I and a DNA encoding the protein of claim 1-10. Under 35 U.S.C. § 121, this restriction indicates that the protein is not obvious over the DNA that encodes it (i.e., that the protein and the DNA are patentably distinct), and that immunoassays are not obvious over the antibody used in the assay. Applicants respectfully request that the Examiner reconsider the restriction requirement imposed in the present application.

The Amendments

The amendments to the specification are submitted to insert material contained on two pages which were unintentionally omitted from the copy of the specification which was filed. The material on these two pages was incorporated by reference from the parent applications (see the last sentence of the first paragraph of the application), and may be found on page 16, lines 1-15, page 23, lines 19-26, page 25, lines 7-14 and the paragraph spanning pages 29 and 30 of Serial No. 07/578,438 and pages 7 and 8 of Serial No. 07/640,497. Therefore, this amendment is only to insert into the specification the actual text of material that was already incorporated by reference. M.P.E.P. § 608.01(p). Thus, no new matter is added to the application by this amendment.

In view of Applicants' traversal of the restriction requirement, amendments are submitted herein to the entire set of claims to maintain consistency with the amendments made in the

provisionally-elected claims. Applicants respectfully request that the entire set of claims be amended as set forth above, whether the restriction is withdrawn and all claims are reconsidered or reconsideration is limited to only the elected claims.

The claims drawn to proteins (original claims 1-8) are amended herein to clearly recite the 30 kDa protein (amended claims 1-4) and the 75 kDa protein (amended claim 5). Amended claims 1 and 2 recite particular properties of the 30 kDa protein that are described in the specification, *inter alia*, on page 14, lines 20-21; page 15, lines 10, 15-16, 19-21, and 24-28; page 16, lines 11-12, 16-22 and 26-29; page 17, lines 1-9; and from page 19, line 29 to page 20, line 1, and are exemplified in Examples 1, 3, 5-6, 10-11, 14-5, 18, and 30. Amended claims 3 and 4 recite particular nucleic acids and their sequences which are disclosed in the specification in Examples 6, 21, and 28. Amended claim 5 recites particular properties of the 75 kDa protein that are described in the specification, *inter alia*, on page 17, lines 22-23 and 25-29, and page 18, lines 1-5, and exemplified in Examples 4 and 17-19. The remaining claims are amended only to make them consistent with amended claims 1-5, without any change in scope other than the description of the protein in the claims from which they depend. The proteins recited in amended claims 1-5 being fully supported in the specification, the remaining amended claims are likewise supported.

Applicants submit that no new matter is added by the above amendments, and respectfully requests that these amendments be entered in the above-named application.

The Invention

The present invention is directed to proteins having growth factor activity exhibited through binding to receptor proteins analogous to the epidermal growth factor receptor (EGFR,

also known as erbB). EGFR is activated by binding of its ligand, epidermal growth factor (EGF) or an analogous protein transforming growth factor alpha (TGFα). A family of proteins analogous to EGFR or erbB have been identified and designated erbB-2, erbB-3, and erbB-4. The erbB analogues are oncogenes, and therefore proteins which control the cellular activities mediated by these receptors are of great interest for use in cancer therapy.

Prior to the work of the present inventors, no factors that activated the analogues of erbB were known. The present inventors have discovered a family of highly homologous proteins of about 30 kDa and another protein of 75 kDa which activate the erbB analogues. The proteins of this invention are structurally distinct from EGF and its known analogue TGFα. The invention is directed to these novel proteins and their diagnostic and therapeutic use.

Utility Rejection

The specification stands objected to and claims 1-20 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of an enabling disclosure. Claims 1-20 stand rejected under 35 U.S.C. § 101 for lack of demonstrated patentable utility. The claims are rejected on the grounds that the claims are drawn to proteins having therapeutic utility and that *in vivo* demonstration of the therapeutic utility is required for patentability. This rejection is respectfully traversed.

It is acknowledged in the Office Action that "the specification exemplifies 2 proteins having molecular weight of 30 kDa and 75 kDa from MDA-MB-231 and SK-BR-3, respectively, and in vitro cell culture inhibition or stimulation." However, it is urged in the Office Action that usefulness of the ligands for affecting cell growth has not been shown because the acknowledged *in vitro* demonstration of the protein effector's effect on cells is urged not to provide convincing evidence that an analogous effect will be observed *in vivo*, due to a variety

of interfering circumstances including plasma stability, immunogenicity, compartmentalization, etc.

Applicants respectfully point out that amended claims 1-5 are drawn to proteins, not therapeutic methods. These proteins are acknowledged in the Office Action to be exemplified in the specification and to have demonstrated biological activity. Furthermore, the proteins are disclosed in the specification to have *diagnostic* utility, based on their ability to show cellular effects *in vitro* on cells that overexpress erbB-2, and their use as competing ligands in competitive immunoassay of biological fluids to detect the presence of the proteins. Therefore the subject matter of claims 1-5 has clear patentable utility.

Experimental procedures based on the claimed methods of stimulating and inhibiting erbB-2 overexpressing cells *in vitro* (claims 9-10, 13-16, and 19-20) are useful for screening drug candidates that may alter the cellular behavior of erbB-2 overexpressing cells. Testing candidate drugs in a quick cell culture assay to see whether they alter the interaction between the claimed proteins and the erbB analogues is a rapid procedure for eliminating candidates which have no effect, thereby reducing the number of trials that need to be run using more complex *in vivo* test systems.

Furthermore, the claimed proteins *do* have demonstrable *in vivo* activity, as shown in the two abstracts attached hereto (Pietras, et al. 1993, *Proc. Am. Assoc. Cancer Res.*, 34:96, Abstr. 573, and Aguilar, et al. 1993, *Mol. Biol. Cell (Suppl.)*, 4:127a, Abstr. 739). Each of the abstracts describes experiments in which subcutaneous injection of the 30 kDa protein of this invention (called heregulin in the abstracts) stimulated the formation of tumors due to growth

of MCF-7 cells in mice relative to control mice which did not receive the injection of the protein.

Applicants submit that the application as filed demonstrates that the claimed proteins and methods of affecting cell growth have patentable utility *in vitro*, and furthermore that the utility asserted in the application based on *in vivo* activity can be demonstrated as shown in the attached abstracts. Therefore Applicants respectfully request that the rejection of claims 1-5, 9-10, 13-17, and 19-20 under 35 U.S.C. §§ 101 and 112, first paragraph, be withdrawn.

Art Rejections

Claims 1-20 stand rejected under 35 U.S.C. 102 (various subsections) as anticipated by or in the alternative as obvious over one or more of thirteen publications. These rejections are respectfully traversed.

The cited publications are grouped below according to the characteristics of the proteins they disclose. The patentability of the amended claims will be discussed with regard to each group.

erbB-2 ligands

Lupu, et al., *Science*, 1990, 249:1552

Lupu, et al., *Am. Assoc. for Cancer Res.* Abstract, 1990

Genentech patent application WO92/20798

Baccus U.S. Patent No. 5,288,477)

With regard to the rejection based on publications describing erbB-2 ligands, Applicants point out that the proteins in these publications are derived from the inventors' disclosure. With the exception of *American Association for Cancer Research* Abstract, all of these publications

were published subsequent to the filing date of the parent application Ser. No. 07/528,438, filed May 25, 1990, from which the inventors claim priority for the rejected subject matter. The *American Association for Cancer Research* Abstract is a publication by the inventor less than one year before the filing date of the priority application. Therefore, none of these publications is a reference against Applicants.

Extracellular Domain (ECD) of erbB-2

Langton, et al., *Canc. Res.*, 1991, 51:2593

Langton discloses a fragment of a receptor molecule from the erbB family, while the present invention is directed to different proteins that bind to receptors of the erbB family. p75 (claim 5) *reverses* the effect of ECD on SK-Br-3 cells, as shown in Example 19, page 79, and thus p75 is distinguishable from ECD. The sequence of gp30 (claims 1-4) is different from that of erbB-2 (see Figures 18 and 23). The claimed proteins are clearly different from the ECD protein.

TGFα

Sherwin, et al., *Canc. Res.*, 1983, 43:403

Stromberg, et al., *J. Cell. Biochem.*, 1986, 32:247

Dickson, et al., *Canc. Res.*, 1986, 46:1707

Lippman, et al., *Breast Cancer Research and Treatment*, 1986, 7:59

These four publications all discuss TGFα, which was compared to gp30 in the Examples of the present application (Examples 5 and 6, pages 63-66) and shown to be structurally different by peptide analysis. Thus, the claimed protein can be easily differentiated from the disclosures of these publications.

Anti-erbB-2 Antibodies

Niman, European Patent 0 354 808

Hudziak, et al., *Mol. Cell. Biol.*, 1989, 9:1165

Langton, et al., *Cancer Res.*, 1991, 51:2593

Goldman, et al., *Biochemistry*, 1990, 29:11024

These publications all disclose immunoglobulins which are large proteins (150,000 kDa in contrast to 30 kDa and 75 kDa for the claimed proteins) and dissociate into multiple subunits of dissimilar molecular weight in reducing SDS PAGE (in contrast to the single band observed for the claimed proteins, Examples 3 and 4, pages 54-62). Thus, the claimed proteins can be easily differentiated from the antibodies disclosed in these publications.

Amphiregulin

Shoyab, et al., U.S. Patent 5,115,096

Shoyab discloses amphiregulin, a protein of 22 kDa, and its amino acid sequence. The sequence of gp30 (claims 1-4) is different from that of amphiregulin (see Figures 18 and 23). Amphiregulin can also be distinguished from p75 based on the relative size of the two proteins. The claimed proteins are clearly different from amphiregulin disclosed by Shoyab.

The claimed proteins may be distinguished structurally from the ECD of erbB-2, antibodies, TGFα, and amphiregulin disclosed in the cited publications. Furthermore, the claims as amended clearly recite characteristics which differ between the claimed proteins and the other proteins disclosed in the cited publications. None of these publications suggest proteins having the structure of Applicants' proteins. With regard to the four cited publications which disclose heregulins, none of them anticipate Applicants disclosure in the earliest parent application from

which priority is claimed. Thus, the proteins claimed in amended claims 1-5, and the methods of using them claimed in amended claims 9-10, 13-17, and 19-20, are novel and non-obvious over the cited publications, and Applicants respectfully request that the rejection of the amended claims under 35 U.S.C. § 102, or in the alternative under 35 U.S.C. § 103, be withdrawn.

Applicants respectfully request that the subject application be reconsidered in view of the amendments and arguments set forth herein.

Respectfully submitted,

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18M1/0628
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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on 3/28/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-5, 9, 10, 13-16, 19-21, 23-27, 33, 34, 36, 37, 40-42 and 44-46 are pending in the application.
   Of the above, claims 21, 23-27, 33, 34, 36, 37, 40-42 and 44-46 are withdrawn from consideration.
2. ☑ Claims 6-8, 11, 12, 17, 18, 22, 28-32, 35, 38, 39, and 43 have been cancelled.
3. ☑ Claims 5, 13, 14, 19 and 20 are allowed.
4. ☑ Claims 1-4, 9, 10, 15 and 16 are rejected.
5. ☐ Claims _____ are objected to.
6. ☑ Claims 1-46 had been are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____. has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

Part III DETAILED ACTION

Applicant's amendments and arguments filed March 20, 1995 have been carefully and fully considered. In view of the fact that the claimed invention is drawn to products and methods of use in vitro cell cultures, the objection under 35 USC 112, first paragraph, and the rejection under 35 USC 112, first paragraph and 35 USC 101 are withdrawn.

1. Applicant's election with traverse of Group I, claims 1-5, 9, 10, 13-16, 19 and 20 in Paper No. 7 filed March 20, 1995 is acknowledged. The traversal is on the ground(s) that the invention group V represents a method for producing protein of Group I and a DNA encoding the protein of claim 1-10. Therefore, Applicant states that under 35 USC 121 this restriction indicates that the protein is not obvious over the DNA that encodes it and that immunoassays are not obvious over the antibody used in the assay. This is not found persuasive because DNA and proteins encoded by the DNA are distinct products and the same DNA may or may not yield the protein it encodes depending on the conditions of expression. Further, the protein need not be prepared recombinantly but may be isolated from the natural sources. Further, an antibody can be used in diagnosis or therapy which are separate and distinct methods for the use of the same compound.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 21, 23-27, 31-34, 36, 37, 40-42 and 44-46 have been withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 7.

3. Applicant's attention is drawn to the fact that the sequence disclosures in the drawings must also comply with the rules set forth under 37 CFR 1.821-1.825.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claim 3 is rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "or a fragment thereof" at the end of the claim is unclear as to its reference to the sequence homology or to the protein claimed. If the phrase is the limitation of the sequences of DNA which encodes protein or the protein, what fragment needs to correspond in order to possess the functional attributes claimed? If it is meant as the protein claimed, such is not clear from the specification as to which fragments are intended as having the functional properties recited.

6. Claims 1-4, 9, 10, 15 and 16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims 1-4 appear to be drawn to the same protein but reciting different functional properties of the same protein. Or are these proteins different? If the claims are drawn to the same protein then the claims are duplicated for the protein and methods of use thereof.

7. Claims 1-4, 9, 10, 15 and 16 are rejected under 35 U.S.C. § 102(a) as being anticipated by Abstr 491 (March 1990).

Lupu et al teach gp30 which binds $p185^{erbD-2}$ and inhibits growth of cells which over express $p185^{erbD-2}$.

8. Claims 1-4 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Sherwin et al (1983) or Dickson et al (1986) or Lippman et al (1986).

All of the references teach EGF like or TGFα like growth factors from conditioned medium of cancer cells such as MCF-7 or MDA-MA-231 having 30 kDa (page 67 of Lippman et al (1986); on page 1707, abstract and page 1710 of Dickson et al (1986); and page 403 of Sherwin et al (1983). The references are silent as to the TGF like factors as being a ligand to erbB-2. Nevertheless, the properties appear to describe the same protein.

9. Claims 1-4, 9, 10, 15 and 16 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Shoyab et al 5,115,096. The reference teaches amphiregulin (AR) having similar function as the instantly claimed erbB-2 ligand. AR is taught by the reference as having cell growth stimulatory or inhibitory activity, AR competes with EGF for binding to EGFR but the growth inhibitory signal generated by AR is initiated by a receptor binding event which does not involve EGFR; has lower affinity to EGFR than EGF (column 29); amino acid sequence is related to several growth factors, most of which belong to the EGF-super family wherein the N-terminal AR sequence resemble TGFα; and are present or can be TPA induced in breast adenocarcinoma (column 39). See columns 11-17. However, the molecular weight disclosed is 22,500 Da although functionally equivalent larger or truncated forms are taught. See column 2. Further, the reference is silent as to the binding specificity to $p185^{erbB-2}$. However, in view of the similarities in the properties and sources this rejection is set forth.

APPLICANT'S ARGUMENTS AND EXAMINER'S RESPONSE :

erbB-2 ligands:

Applicant states that Lupu, et al Science, 1990, 249:1552; Lupu et al (1990, abstr); WO92/20798 and Baccus 5,288,477 have derived the erbB-2 ligands from instant inventor's disclosure. Applicant contends that with exception of the Lupu et al (1990, abstr), all of the references have been published subsequent to the filing date of the parent application Ser. No.

07/528,438, filed May 25, 1990. Further, Applicant urges that the abstract is a publication by the inventor less than one year before filing date of the priority application.

However, the amended claims recite the amino acid sequence information which is lacking in written description in the parent 07/528,438. Therefore, the following rejections are maintained in the absence of verified statements that the gp30 protein disclosed in the parent 07/528,438 is the same protein which had been used to obtain the sequence set forth in the instant application.

Claims 1-4 are rejected under 35 U.S.C. § 102(a) as being anticipated by Vandlen WO 92/20798.

The patent discloses heregulins which the specification states as the same ligand as that of Applicant's. See the entire patent and see page 14, line 27 of the specification.

Claims 1-4, 9, 10, 15 and 16 are rejected under 35 U.S.C. § 102(a or b or f or e) as being anticipated by Lupu et al (Science 249: 1552-1555) (1990) or Abstr 491 (March 1990) or Bacus 5,288,477.

Lupu et al teach gp30 which binds $p185^{erbB-2}$ and inhibits growth of cells which over express $p185^{erbB-2}$. See the entire article pages 1552-1554. Bacus teach the use of gp30 of Lupu et al. See columns 17-18.

Further, the abstract number 491 has authors which differ from the inventors. Therefore, even if the effective filing date goes back to the parent 07/528,438 , it is a proper art as work of others under 35 USC 102(a).

Extracellular Domain (ECD) of erbB-2:

Applicant urges that Langton, et al, Cancer Res., 1991, 51:2593.disclose a fragment of a receptor from the erbB family, while the present invention is directed to different

proteins that bind to receptors of the erbB family. In view of such, the rejection is withdrawn over Langton et al.

TGFα:

Applicant urges that Sherwin et al, Stromberg et al, Dickson et al, and Lippman et al discuss TGFα which had been compared to gp30 in the Examples of the present application at Examples 5 and 6, pages 63-66 and shown to be structurally different by peptide analysis.

However, the references distinguishes these proteins as "TGFα-like", not TGFα, having molecular weight 30,000da which terminology was also used in the parent application to describe the same from TGFα having molecular weights 6000-8000 da. As such the arguments are not deemed persuasive. Stromberg et al is withdrawn as the reference does not recite protein having 30Kda.

Anti-erbB-2 antibodies:

The references are withdrawn in view of the amendments.

Amphiregulin:

Applicant urges that Shoyab et al 5,115,096 discloses amphiregulin, a protein of 22 KDa and its amino acid sequence which sequence is different from gp30. Since the non-glycosylated protein of the instant claims are allegedly 22 Kda and the functional properties taught by the reference appear similar, this rejection is maintained. The claimed invention is not limited to those sequences disclosed in the Figures 18 and 23 of this application.

10. Applicant's amendment necessitated the new grounds of rejection. Accordingly, THIS ACTION IS MADE FINAL. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group Art Unit 1813 Fax number is (703) 305-7939 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay K.A. Kim, Ph. D. whose telephone number is (703) 308-3881. The examiner can normally be reached on Monday-Thursday from 7:00 AM-4:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christine Nucker, can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

June 23, 1995

Kay K.A. Kim, Ph.D.
Primary Examiner
Group 1800